

Stereoselective Reduction of Amino Ketone with Sodium Borohydride in the Presence of Metal Chloride. A Simple Pathway to *S*-Propranolol

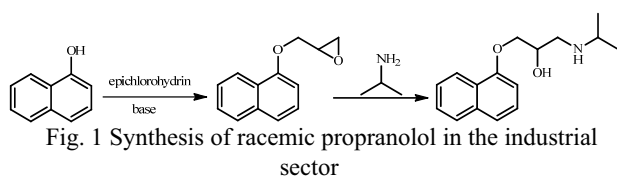
R. Inkum, A. Teerawutgulrag, P. Puangsombat, N. Rakariyatham

Abstract—Propranolol is worldwide hypertension drug that is active in *S*-isomer. Patients must use this drug throughout their lives, and this action employs a significant level of expenditure. A simpler synthesis and lower cost can reduce the price for the patient. A simple synthesis pathway of *S*-propranolol starting from protection of (*R,S*)-propranolol with di-*t*-butyldicarbonate and then the product is oxidized with pyridiniumchlorochromate. The selective reduction of ketone occurs with sodiumborohydride in the presence of metal chloride provided *S*-propranolol.

Keywords—*S*-propranolol, selective reduction, sodium borohydride, metal chloride

I. INTRODUCTION

PROPRANOLOL is a prescribed medicines belonging to a class of compounds known as beta-blockers, which are used to treat hypertension, angina pectoris, glaucoma, anxiety, obesity and other cardiovascular diseases [1,2]. Nowadays, these drugs are available in the market in racemate form, in which only the *S*-enantiomer has beta-adrenergic blocking activity [3-6], while the *R*-form merely has a membrane stabilizing effect and is 130 times less active than the *S*-analogue [3]. While reports of various methods have been published for synthesizing *S*-propranolol including usage of enzymes for resolution [7], asymmetric hydrogenation with chiral metal complex catalyst [8], asymmetric epoxidation of allyl alcohol [9] and sorbitol [10], employing a polymer supported reagent [11], as well as using $Zn(NO_3)_2$ and (+)-tartaric acid induction in the ring opening step [12]. Several researchers have reported on the synthesis of (*S*)-propranolol *via* lipase catalyzed reaction [13-16] and in the presence of cyclodextrins [17]. However, the multiple steps in each procedure and high cost of the initial materials have increased the cost of manufacturing. In pharmaceutical manufacturing, racemic propranolol is synthesized using epichlorohydrin (Fig. 1) [7b] as a substrate.



Rachaneebhorn Inkum is a graduate student in Doctor of Philosophy (Ph.D) with Department of Chemistry, Faculty of Science, Chiang Mai University, Chiang Mai, Thailand (e-mail: rachaneebhorn@hotmail.com).

Aphiwat Teerawutgulrag, Pakawan Puangsombat and Nuansri Rakariyatham are with Department of Chemistry, Faculty of Science, Chiang Mai University, Chiang Mai, Thailand.

Herein we report a straightforward method for preparation of *S*-propranolol from the racemate *via* selective reduction, which is considered both a simple and inexpensive procedure (Fig. 2).

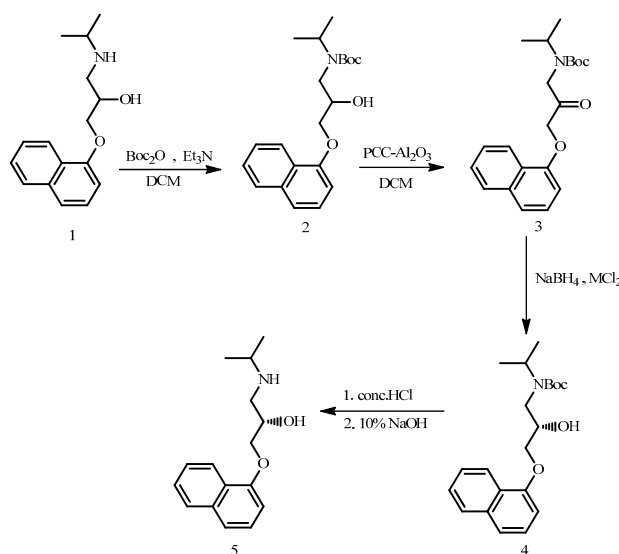


Fig. 2 Synthesis of *S*-propranolol from racemate

II. EXPERIMENTAL METHODS

A. Materials

(*R,S*)-propranolol was extracted from propranolol that is available in the market. Pyridiniumchlorochromate and metal chloride were purchased from Aldrich Chemistry. Sodium borohydride was purchased from Labchem. All chemicals and reagents were of analytical reagent grade. Thin-layer chromatography (TLC) was utilized on silica plates 60 F₂₆₄ and column chromatography was carried out in 0.063-0.20 mm silica gel. HRMS analysis was performed on ESI-Q-TOF-MS (Micromass, Manchester, UK). IR spectra were reported on a FT-IR spectrometer (Tensor 27). ¹H-NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer, using trimethylsilane as an internal standard. Specific rotation was measured on a ADP 220 polarimeter (Bellingham + Stanley Limited, Tunbridge wells, England).

B. Synthesis of *S*-propranolol

t-butyl(2-hydroxy-3-(naphthalen-1-yloxy)propyl) (isopropyl) carbamate (2)

To (*R,S*)-propranolol **1** (2.19 g, 8.46 mmol) and triethylamine (1.41 ml, 10.1 mmol) in dichloromethane (25 ml)

at 0 °C, Boc₂O (2.20 ml, 10.1mmol) was added by stirring. The mixture was warmed to room temperature and stirred overnight. The reaction was washed with 10% NaOH and extraction was done with ethyl acetate (3x50 ml). The organic layer was dried with anhydrous sodium sulphate then concentrated under reduced pressure. The residue was purified by column chromatography with neat hexane as an eluent to give *t*-butyl (2-hydroxy-3-(naphthalen-1-yloxy)propyl)(isopropyl) carbamate (2) (2.96 g, 98%) as a pale yellow oil.

t-butylisopropyl(3-(naphthalen-1-yloxy)-2-oxopropyl)carbamate (3)

t-butyl (2-hydroxy-3-(naphthalen-1-yloxy)propyl)(isopropyl) carbamate (2) (0.2 g, 0.56mmol) was dissolved in dichloromethane (10 ml) and pyridiniumchlorochromate(0.24 g, 1.12mmol) was added at 0 °C and warmed to room temperature. After refluxing overnight, the mixture was cooled and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography eluted with gradient 5% ethylacetate-hexane to give *t*-butyl isopropyl(3-(naphthalen-1-yloxy) -2-oxopropyl) carbamate (3)(0.16 g, 81%) as a paleyellow oil.

S-*t*-butyl (2-hydroxy-3-(naphthalen-1-yloxy)propyl)(isopropyl) carbamate (4)

A solution of *t*-butyl isopropyl(3-(naphthalen-1-yloxy) -2-oxopropyl) carbamate (3) (0.20 g, 0.56 mmol), and magnesium chloride(0.23 g, 1.12mmol)in methanol (4 ml) was stirred at room temperature for 30 min. Then sodium borohydride(0.021 g, 0.56mmol) was added proportionately. After the reaction was completed, water was added and extracted with ethyl acetate (3x20 ml). The organic layer was dried with anhydrous sodium sulphate and concentrated under reduced pressure. The crude mixture was purified by column chromatography eluted with 20% ethylacetate-hexane to give *S*-*t*-butyl (2-hydroxy-3-(naphthalen-1-yloxy)propyl)(isopropyl) carbamate(4)(0.194 g, 96%) as a pale yellow oil.

S-propranolol (5)

S-*t*-butyl (2-hydroxy-3-(naphthalen-1-yloxy)propyl)(isopropyl) carbamate(4) (0.194 g, 0.54mmol) was dissolved in ethanol (3 ml) andconcentrated HCl(excess) was added drop wise at 0 °C and stirred for 2 h. After the reaction was completed, water was added and basicified with 10% sodium hydroxide, the resulting mixture was extracted with ethyl acetate (3x20 ml).The organic layer was dried with anhydrous sodium sulphateand concentrated under reduced pressure. The product was purified by recrystallization with hexane to give *S*-propranolol (5)(0.1357 g, 97%) as a white solid.

C. Selective Reduction of *t*-butyl isopropyl(3-(naphthalen-1-yloxy) -2-oxopropyl) carbamate (3)

The reduction of the compound (3) with sodium borohydride in the presence of various forms of metal chloride at 0 °C in methanol was examined.

D. Deprotection of *S*-*t*-butyl (2-hydroxy-3-(naphthalen-1-yloxy)propyl)(isopropyl) carbamate (4)

The deprotection of the compound (4), which was obtained from selective reduction in the presence of various forms of metal chloride, occurred by concentrated hydrochloric acid. The absolute configuration [α]_D and enantiomeric excess (%ee) of selective reduction were determined by correlating the data with those reported in the literature [7b].

III. RESULTS ANDDISCUSSION

A. Selective Reduction of *t*-butyl isopropyl(3-(naphthalen-1-yloxy) -2-oxopropyl) carbamate (3)

Togetheress of metal chloride accelerated the reaction and increased the formation of alcohol product (compound 4). The reaction required 30 min at 0 °C. The yields of this step are shownin Table I.

TABLE I
SELECTIVE REDUCTION OF (3) IN A PRESENCE OF METAL CHLORIDE

Entry	MCl ₂	%YIELD
1	-	95
2	MgCl ₂	96
3	CaCl ₂	88
4	SrCl ₂	91
5	BaCl ₂	93

B. Deprotection of *S*-*t*-butyl (2-hydroxy-3-(naphthalen-1-yloxy)propyl)(isopropyl) carbamate (4)

Going down the periodic table of alkaline earth metallic chlorides, enantiomeric excess (%ee) decreased. The result might be explained by the formation of the rigid transition state for the metal chloride which has a small ionic radius as schematically described in Fig. 3[18].

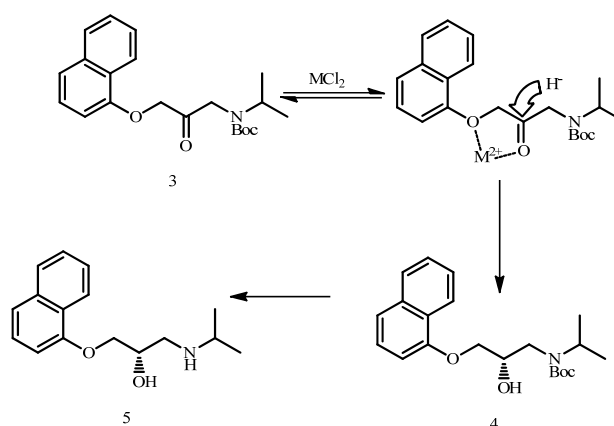


Fig. 3 The formation of a rigid transition state for metal chloride

The ionic radius of metal and were as follows: Mg²⁺ 0.86 Å; Ca²⁺ 1.14 Å; Sr²⁺ 1.32 Å; Ba²⁺ 1.49 Å. The %ee of products (5) are shown in Table II.

TABLE II
DEPROTECTION OF (4) IN A PRESENCE OF METAL CHLORIDE

Entry	MCl ₂	%YIELD	%ee
1	-	95	27.46
2	MgCl ₂	97	68.65
3	CaCl ₂	93	36.62
4	SrCl ₂	93	27.76
5	BaCl ₂	94	27.30

t-butyl (2-hydroxy-3-(naphthalen-1-ylloxy)propyl)(isopropyl)carbamate (2)

IR (neat), ν_{\max} , 3379, 3056, 2973, 1685, 1403; ¹H-NMR (400 MHz, CDCl₃) 1.20 (6H, dd, $J = 6.821$ Hz, 6.568 Hz), 1.52 (9H, s), 3.46-3.60 (2H, m), 4.00-4.13 (1H, m), 4.14-4.32 (3H, m), 5.02-5.24 (1H, br), 6.85 (1H, d, $J = 7.579$ Hz), 7.38 (1H, t, $J = 7.579$ Hz), 7.42-7.54 (3H, m), 7.78-7.85 (1H, m), 8.20-8.28 (1H, m); ¹³C-NMR (100 MHz, CDCl₃) 154.1, 134.4, 127.5, 126.3, 125.8, 125.1, 121.6, 120.5, 104.7, 80.6, 71.9, 69.8, 49.5, 48.6, 47.0, 28.4, 20.9; HRMS calcd for C₂₁H₂₉NO₄[M+Na]⁺ 382.1994, found 382.2003.

t-butylisopropyl(3-(naphthalen-1-ylloxy)-2-oxopropyl)carbamate (3)

IR (neat), ν_{\max} , 3058, 2976, 2930, 1692, 1399, 1166; ¹H-NMR (400 MHz, CDCl₃) 1.20 (6H, dd, $J = 6.821$ Hz), 1.40 (9H, s), 4.20 (1H, s), 4.45-4.58 (1H, m), 4.80 (1H, s), 6.73 (1H, d, $J = 7.831$ Hz), 7.36 (1H, t, $J = 7.831$ Hz), 7.45-7.60 (3H, m), 7.78-7.88 (1H, m), 8.29-8.36 (1H, m); ¹³C-NMR (100 MHz, CDCl₃) 202.9, 154.6, 153.4, 134.6, 127.6, 126.7, 125.7, 125.5, 121.6, 121.3, 104.9, 80.1, 72.2, 49.1, 48.7, 28.2, 20.4; HRMS calcd for C₂₁H₂₇NO₄[M+Na]⁺ 380.1838, found 380.1826.

S-*t*-butyl (2-hydroxy-3-(naphthalen-1-ylloxy)propyl)(isopropyl)carbamate (4)

All data are accordance with compound (2).

S-propranolol (5)

IR (KBr), ν_{\max} , 3477, 3275, 2964, 1628, 1265; ¹H-NMR (400 MHz, CDCl₃) 1.03 (6H, d, $J = 6.316$ Hz), 2.73-2.82 (2H, m), 2.89-2.95 (1H, m), 4.03-4.14 (3H, m), 6.75 (1H, d, $J = 6.568$ Hz), 7.29 (1H, t, $J = 7.579$ Hz), 7.35-7.45 (3H, m), 7.70-7.75 (1H, m), 8.15-8.19 (1H, m); ¹³C-NMR (100 MHz, CDCl₃) 154.4, 134.5, 127.5, 126.4, 125.8, 125.2, 121.8, 120.6, 104.9, 70.7, 68.6, 49.5, 48.9, 23.2, 23.0; HRMS calcd for C₁₆H₂₁NO₂[M+1]⁺ 260.1650, found 260.1651. mp. 90-92 °C.; %ee 68.65 %

IV. CONCLUSION

The selective reduction of ketone compound (3) with sodium borohydride in the presence of various forms of metal chloride can produce *S*-propranolol. This method is considered both convenient and economical enough to proceed with.

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Rachaneebhorn Inkum received her Bachelor's Degree in Chemistry from Chiang Mai University, Thailand in 1999 and her Master's degree in Chemistry (Organic Chemistry) from Chiang Mai University, Thailand in 2003. She is presently working as a lecturer in the Department of Science, Faculty of Science and Agricultural Technology, Rajamangala University Technology Lanna Nan, Thailand. Her main research interests are in the organicsynthesis of drugs and pheromone and methodology.

Asst.Prof.Dr. Aphiwat Teerawutgulrag received his Bachelor's Degree in Chemistry (1st class honour) from Chiang Mai University, Thailand in 1991; Master's Degree and Doctor of Philosophy (Ph.D.) Degree in Organic Chemistry from The University of Manchester, Manchester, United Kingdom in 1996. He is presently working as a lecturer in the Department of Chemistry, Faculty of Science, Chiang Mai University, Chiang Mai, Thailand. His main research interests are in organic synthesis, essential oil isolation and forensic chemistry

Dr. Pakawan Puangsombat received her Bachelor's Degree in Chemistry (1st class honour) from Chiang Mai University, Thailand in 1991 and her Doctor of Philosophy (Ph.D.) degree in Organic Chemistry from Keele University, Staffordshire, United Kingdom in 1996. She is presently working as a lecturer in the Department of Chemistry, Faculty of Science, Chiang Mai University, Chiang Mai, Thailand. Her main research interests are in chemical compositions and bioactive substances from Thai plants.

Assoc.Prof.Dr. Nuansri Rakariyatham received her Bachelor's Degree in Chemistry from Chiang Mai University, Thailand in 1975 ;her Master's degree in biochemistry from Mahidol University, Bangkok, Thailand in 1977 and Doctorat detroisieme cycle en nutrition et alimentation, Universite de Bordeaux, France, in 1985. She is presently working as lecturer in Department of Chemistry, Faculty of Science, Chiang Mai University, Chiang Mai, Thailand. Her main research interests are biochemistry and biotechnology.